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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/585,754
Filing Date: July 12, 2006
Appellant(s): FRANCOIS ET AL.

Jeremy K McKown
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/23/2011 appealing from the Office action mailed 10/29/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application: Claims 1 and 3-12.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken is being maintained by the examiner.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

WO 96/13499	Heeres	5-1996
U.S. 2002/0147201	Chen	10-2002

Basit et al., The Effect of Polyethene Glycol on Gastrointestinal Transit: Implications for the Formation of Poorly Water Soluble Drugs, Pharmaceutical Research, Volume 18, No. 8, 2001.

(9) Grounds of Rejection

Claims 1 and 3-12 are under 35 U.S.C. 103(a) as being unpatentable over Heeres (WO 96/13499- See IDS dated 7/12/2006) in view of Basit et al. (The Effect of Polyethylene Glycol 400 on Gastrointestinal Transit: Implications for the Formation of

Poorly Water Soluble Drugs, Pharmaceutical Research, Volume 18, No. 8, 2001), the combination further in view of Chen (2002/0147201).

Heeres teaches a composition which may be in the form of a solution and is preferably for oral administration (p.10, lines 7-9). The composition may contain and active ingredient as well as glycols, sugars, and other common pharmaceutical media (i.e. additives) (p.10, lines 3-14). Mitratapide is disclosed to be an active ingredient (p.17, Compound 22). Oral additives include taste modifiers such as sodium saccharin. Heeres also teaches that when the composition is formulated for parenteral administration, other ingredients may be included to aid in solubility (p.10. lines 16-18). Heeres also teaches that acid addition salts of the compounds of formula (I) are obviously more suitable in the preparation of aqueous compositions due to their increased water solubility over the base form (p.10, lines 28-30).

Heeres does not teach the incorporation of an antioxidant or a specific component which will increase the solubility of the mitratapide active agent.

Basit teaches that PEG 400 is a particularly preferred solubility enhancer for poorly water-soluble drugs because in addition to its superior ability to increase solubility of such drugs, PEG 400 concurrently reduces gastrointestinal transit time (Page 1149, Column 2). Therefore, PEG 400 is not only an inert pharmaceutical excipient (Page 1149, Column 2), but also has a positive effect on the bioavailability of the co-administered drug (Page 1149, Column 2).

Basit does not teach the inclusion of mitratapide.

Chen teaches the antioxidant butylated hydroxyanisole (BHA) is commonly included at 0-15% by weight to stabilize compositions (¶76). If the composition is for oral administration, it should have a preferable taste (¶7). Taste modifying agents are commonly employed for this purpose and may come in a variety of forms including sweeteners such as sucrose or sucralose at 0 to 10% by weight (Paragraph 61). Also, cyclodextrins may be included in the composition (¶75).

Chen does not teach the inclusion of mitratapide.

It would have been obvious to one of ordinary skill in the art to use solubility enhancing additives to the oral compositions of Heeres, given that Heeres teaches parenteral formulations can include ingredients to aide in solubility and that more soluble active ingredient salts are preferred. More specifically, Heeres teaches compatible solubility agents include polyethylene glycol, albeit for use as parenteral delivery. The concept of increasing solubility in aqueous forms is relevant to all aqueous compositions, regardless their specifically stated administration form, where it is well known in the art that by increasing solubility, a lower dosage amount is required, thereby easing administration. In choosing additives to aid in solubility, the skilled artisan would have found it obvious to use the specific glycol of Basit, i.e. PEG 400, given that Heeres calls for the addition of glycols and Basit teach PEG 400 to be a known solubility enhancer which also provides additional benefits compared to other glycols.

Further, when choosing other common additives for oral administration, the skilled artisan would have found it obvious to incorporate the additives taught by Chen,

given that Chen teaches these additives result in a composition having increased solubility and bioavailability of the active agent. Specifically, it would have been obvious to complex the active agent with glycyrrhizin, as taught by Chen to increase the solubility of the active ingredient.

Further yet, it would have been obvious to incorporate other taste modifying agents, such as sucralose, as disclosed by Chen, given that the Heeres teaches the incorporation of taste modifying agents. See MPEP 2143(A).

Note, while the “pharmaceutically acceptable solvent” is defined in instant claim 1 as a selection from the recited Markush group, the claim is modified by the transition phrase "comprising", therefore the composition may have an additional pharmaceutically acceptable solvent, such as water, in combination with the specifically recited pharmaceutically acceptable solvent.

With regard to the recitation of a “a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5mg/ml or higher”, it is noted that the instant specification states that "[t]he pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher is preferably selected from the group consisting of ...polyethyleneglycol 400" (Instant specification at p.3, lines 31-36, ¶12).

(10) Response to Argument

First, Appellants argue that Heeres does not specifically link the “laundry list” of dosage forms to mitratapide (Appeal Brief at p.6, 1st paragraph).

Second, Appellants argue that the passage in Heeres suggesting the addition of ingredients to aid in solubility is specific to parenteral compositions rather than applicable to oral compositions (Appeal Brief at p.6, 2nd paragraph). Applicants argue that based on the different adjuvants in example 8 - oral solutions and example 11 - injectable solutions, Heeres did not intend for the teaching of solubility enhancers to be applied to oral solutions.

Third, Appellants argue that Basit teaches away from using PEG 400 by stating that PEG 400 "by means of reducing residence time in the small intestine, is therefore likely to have a detrimental effect on the rate and/or extent of absorption of drugs" (Appeal Brief at p.8, 2nd and 3rd paragraphs citing Basit at p.1149, right col.). Applicants also argue that in light of Basit, the use of PEG 400 is unpredictable (Appeal Brief at p.8, 2nd paragraph).

Fourth, Applicants argue that the relevant claim language "an oral solution of mitratapide that has a solubility of 5 mg/ml or higher at a temperature of 22°C" was ignored by the examiner because the feature was not addressed in the latest Office action (Appeal Brief at p.9, 1st full paragraph). Applicants note that table 1 shows that not all pharmaceutical solvents are useful to achieve such a purpose (Appeal Brief at p.9, 1st full paragraph).

Examiner disagrees. First, while Heeres does teach a broad disclosure including many species of active compounds, the reference actually reduces to practice about 140 compounds. Thus, when formulating the composition of Heeres, the skilled artisan would find it obvious to choose an active ingredient from the 140 or so active

ingredients, each having a common core structure, specifically disclosed in the Heeres reference. The skilled artisan would have a reasonable expectation of success in doing so because Heeres specifically teaches formulating the compositions with a compound of formula 1 and mitratapide is one of the 140 or so compounds within the genus of formula 1 whose structure is specifically disclosed by Heeres.

Second, Heeres teaches that "for parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid in solubility, may be included" (Heeres at p/10, lines 7-9). One of ordinary skill in the art would recognize that the same teaching would apply to oral solutions where it is desired that the solubility be increased, for example, to increase the concentration of the active ingredient. Accordingly, when looking to "example 8-oral solution", the solution contains 1 mg/ml of active ingredient (p.26, last line), while the solution of "example 11-injectible solution" contains the solubilizing agent propylene glycol the active ingredient at 4 mg/ml (p.27, last sentence). Given such data and the fact that it is well known in the art that increasing the concentration of an active ingredient reduces the amount required to be administered to a patient for treatment, thereby easing administration and increasing patient compliance, the skilled artisan would have found it obvious to add a solubilizing agent to an oral solution in order to allow for increased concentration of the active ingredient.

Third, Basit teaches that poorly water-soluble drugs are routinely solubilized using PEG 400 and presented in the form of soft gelatin capsules or simple liquid formulations to enhance their bioavailability (p.1146, introduction). While Basit also

discusses the fact that PEG 400 can reduce the residence time of the drug in the small intestine, it does not teach away from use of PEG 400 as a solubilizer. Rather Basit cautions that for some drugs that are absorbed predominantly in the small intestine, the decreased small intestinal transit time may limit the opportunity for drug absorption, and thus the point of Basit is that PEG 400 cannot be considered a completely inert pharmaceutical excipient. Given that Basit teaches PEG 400 is a well known solubilizing agent and Heeres teaches the use of PEG, generally, for solubilizing active ingredients, it would have been obvious to choose PEG 400 as the specific PEG when formulating the composition of Heeres.

Fourth, polyethylene glycol 400 (PEG 400) is specifically listed as a pharmaceutically acceptable solvent wherein mitratapide has a solubility of 5 mg/ml or higher (Instant Specification at p.3, paragraph 12).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/ADAM C MILLIGAN/

Examiner, Art Unit 1612

Conferees:

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612

/Sharmila Landau/

Supervisory Patent Examiner, Art Unit 1611